

What is claimed is:

SUB A1

~~1. An antisense compound 8 to 30 nucleobases in length targeted to the 5' untranslated region, coding region, intron:exon junction, intron region, exon region, translation termination codon region or 3' untranslated region of a nucleic acid molecule encoding mdm2, wherein said antisense compound modulates the expression of mdm2.~~

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~~2. The antisense compound of claim 1 wherein said antisense compound inhibits the expression of human mdm2.~~

~~3. The antisense compound of claim 1 which is an antisense oligonucleotide.~~

SECRET

~~4. An antisense compound up to 30 nucleobases in length comprising at least an 8-nucleobase portion of SEQ ID NO: 3, 4, 5, 7, 10, 15, 17, 18, 19, 21, 36, 42, 52, 54, 59, 60, 61, 62, 64, 66, 67, 68, 69, 70, 72, 73, 74, 75, 77, 78, 80, 81, 84, 88, 90, 96, 98, 103, 105, 109, 111, 114, 117, 118, 120, 121, 124, 126, 127, 129, 130, 137, 145, 147, 151, 154, 156, 158, 160, 165, 171, 175, 177, 178, 180, 182, 183, 184, 186, 188, 189, 191, 192, 193, 195, 196, 197, 199, 200, 201, 203, 206, 210, 212, 215, 216, 218, 221, 225, 231, 235, 241, 243, 245, 246, 249, 251, 254, 256, 258, 260, 264, 268, or 373 which inhibits the expression of mdm2.~~

~~5. The antisense compound of claim 2 which is targeted to the 5' untranslated region of the S-mdm2 transcript.~~

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~~6. The antisense compound of claim 1 which contains at least one phosphorothioate intersugar linkage.~~

~~7. The antisense compound of claim 1 which has at least one 2'-O-methoxyethyl modification.~~

~~8. The antisense compound of claim 1 which contains at least one 5-methyl cytidine.~~

9. The antisense compound of claim 8 in which every 2'-O-methoxyethyl modified cytidine residue is a 5-methyl cytidine.

10. A pharmaceutical composition comprising the antisense compound of claim 1 and a pharmaceutically acceptable carrier or diluent.

11. The pharmaceutical composition of claim 10 wherein said pharmaceutically acceptable carrier or diluent further comprises a lipid or liposome.

12. A method of modulating the expression of mdm2 in cells or tissues comprising contacting said cells or tissues with the antisense compound of claim 1.

13. A method of reducing hyperproliferation of human cells comprising contacting proliferating human cells with the antisense compound of claim 2 or a pharmaceutical composition comprising said antisense compound.

14. A method of treating an animal having a disease or condition associated with mdm2 comprising administering to said animal a therapeutically or prophylactically effective amount of an antisense compound of claim 1.

15. The method of claim 14 wherein the disease or condition is associated with overexpression of mdm2 and the antisense compound inhibits the expression of mdm2.

16. The method of claim 14 wherein the disease or condition is associated with amplification of the mdm2 gene and the antisense compound inhibits the expression of mdm2.

17. The method of claim 14 wherein the disease or condition is a hyperproliferative condition and the antisense compound inhibits the expression of mdm2.

18. The method of claim 17 wherein the hyperproliferative condition is cancer.

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19. The method of claim 18 wherein the cancer is a blood, bone, brain, breast, lung or a soft tissue cancer.

20. The method of claim 17 wherein the hyperproliferative condition is psoriasis, fibrosis, atherosclerosis or restenosis.

21. The method of claim 14 wherein said antisense compound is administered in combination with a chemotherapeutic agent to overcome drug resistance.

22. An antisense compound up to 30 nucleobases in length targeted to the translational start site of a nucleic acid molecule encoding human mdm2, wherein said antisense compound inhibits the expression of said human mdm2 and comprises at least an 8-nucleobase portion of SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 69, SEQ ID NO: 70 or SEQ ID NO: 72.

23. The antisense compound of claim 22 which contains at least one phosphorothioate intersugar linkage.

24. The antisense compound of claim 22 which has at least one 2'-O-methoxyethyl modification.

25. The antisense compound of claim 22 which contains at least one 5-methyl cytidine.

26. The antisense compound of claim 25 in which every 2'-O-methoxyethyl modified cytidine residue is a 5-methyl cytidine.

27. A pharmaceutical composition comprising the antisense compound of claim 22 and a pharmaceutically acceptable carrier or diluent.

28. The pharmaceutical composition of claim 27 wherein said pharmaceutically acceptable carrier or diluent comprises a lipid or liposome.

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29. A method of modulating the expression of human mdm2 in cells or tissues comprising contacting said cells or tissues with the antisense compound of claim 22.

30. A method of reducing hyperproliferation of human cells comprising contacting proliferating human cells with the antisense compound of claim 22.

31. A method of reducing hyperproliferation of human cells comprising contacting proliferating human cells with the pharmaceutical composition of claim 27.

32. A method of treating an animal having a disease or condition associated with mdm2 comprising administering to said animal a therapeutically or prophylactically effective amount of the antisense compound of claim 22.

33. The method of claim 32 wherein the disease or condition is associated with overexpression of mdm2 and the antisense compound inhibits the expression of mdm2.

34. The method of claim 32 wherein the disease or condition is associated with amplification of the mdm2 gene and the antisense compound inhibits the expression of mdm2.

35. The method of claim 32 wherein the disease or condition is a hyperproliferative condition and the antisense compound inhibits the expression of mdm2.

36. The method of claim 35 wherein the hyperproliferative condition is cancer.

37. The method of claim 36 wherein the cancer is a blood, bone, brain, breast, lung or a soft tissue cancer.

38. The method of claim 35 wherein the hyperproliferative condition is psoriasis, fibrosis, atherosclerosis or restenosis.

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39. The method of claim 32 wherein said antisense compound is administered in combination with a chemotherapeutic agent to overcome drug resistance.

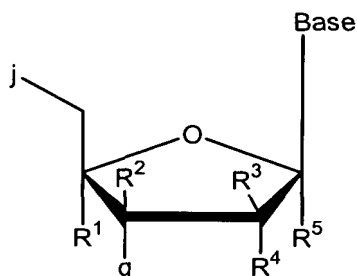
40. A method of modulating apoptosis in cells or tissues comprising contacting said cells or tissues with the compound of claim 1 so that apoptosis is modulated.

41. A method of modulating apoptosis in cells or tissues comprising contacting said cells or tissues with the compound of claim 22 so that apoptosis is modulated.

42. A method of inducing the expression of p21 in cells or tissues comprising contacting said cell with the compound of claim 1 so that p21 expression is increased.

43. A method of inducing the expression of p21 in cells or tissues comprising contacting said cells or tissues with the compound of claim 22 so that p21 expression is increased.

44. An oligonucleotide comprising at least one nucleotide comprising a heterocycle member covalently bound to a substituted sugar member which is further covalently bound through at least one linker to a sugar moiety member of a second nucleotide, said at least one modified nucleotide described according to structure I;



I

j and q are each independently covalently linkers of about 1-15 atoms selected from the group comprising

phosphorothioates, methylene(methylimino), phosphodiester, morpholino, amide, thioamide, polyamide, $(CH_2)_n(G)N(R^{11})$, $(G)N(R^{11})$, $(CH_2)_nN(G)R^{11}$, $N-(CH_2)_n(G)R^{11}$ and

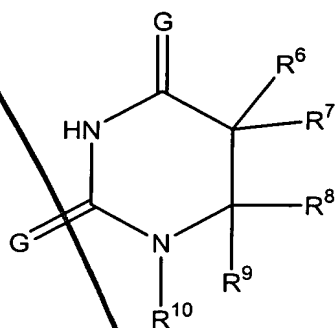
$(CH_2)_nN(R^{11})C(G)$ where G is a heteroatom, n is an integer between about 0 and 5 and each R^{11} is independently selected from the group comprising alkyl, heteroalkyl, cyclic alkyl, heterocycle, aryl, heteroaryl and hydrogen;

R^1 , R^2 , R^3 , R^4 and R^5 are each independently selected from the group comprising halo, hydrogen and GR^{11} and;

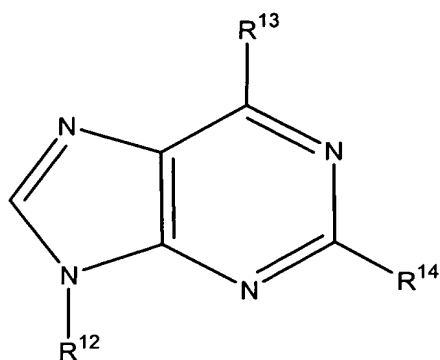
where Base is a nucleobase selected from the group comprising structure II, structure III or structure IV;

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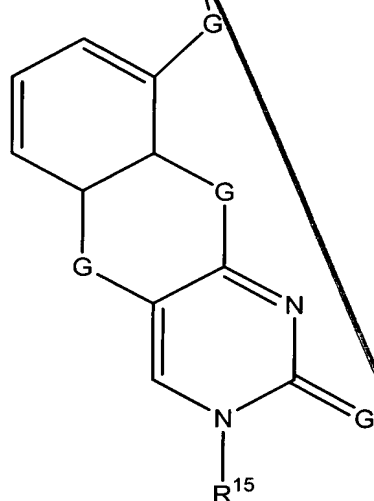
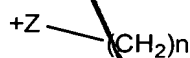
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II



III



IV

where R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴ and R¹⁵ are independently selected from members of the group comprising alkyl, heteroalkyl, cyclic alkyl, heterocycle, aryl, heteroaryl, halo and hydrogen, and;

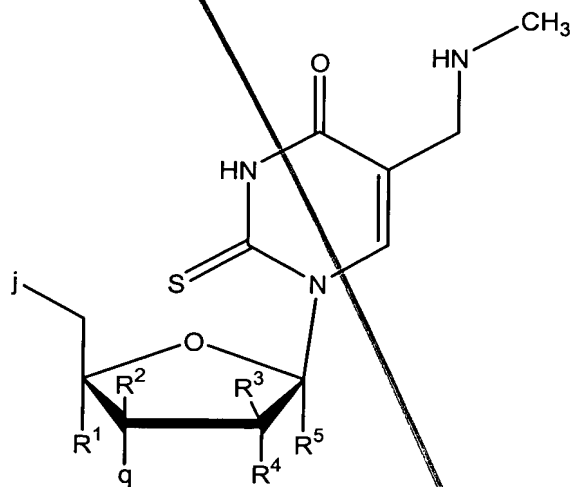
where G is a heteroatom and Z⁺ is a hypervalent species selected from the group comprising a quaternary amine, a cationic alkyl oxygen member, an alkyl sulfonium member or an alkyl phosphonium member and;

where at least one of R¹, R², R³, R⁴, R⁵, R¹⁰, R⁹, R⁸, R⁷, R⁶, R¹², R¹³, R¹⁴ or R¹⁵ is substituted, forming thereby said modified nucleotide.

45. The oligonucleotide according to claim 44 wherein G is O and R⁴ is 2'-O-dimethylamine oxyethylene and the Base is according to structure II;

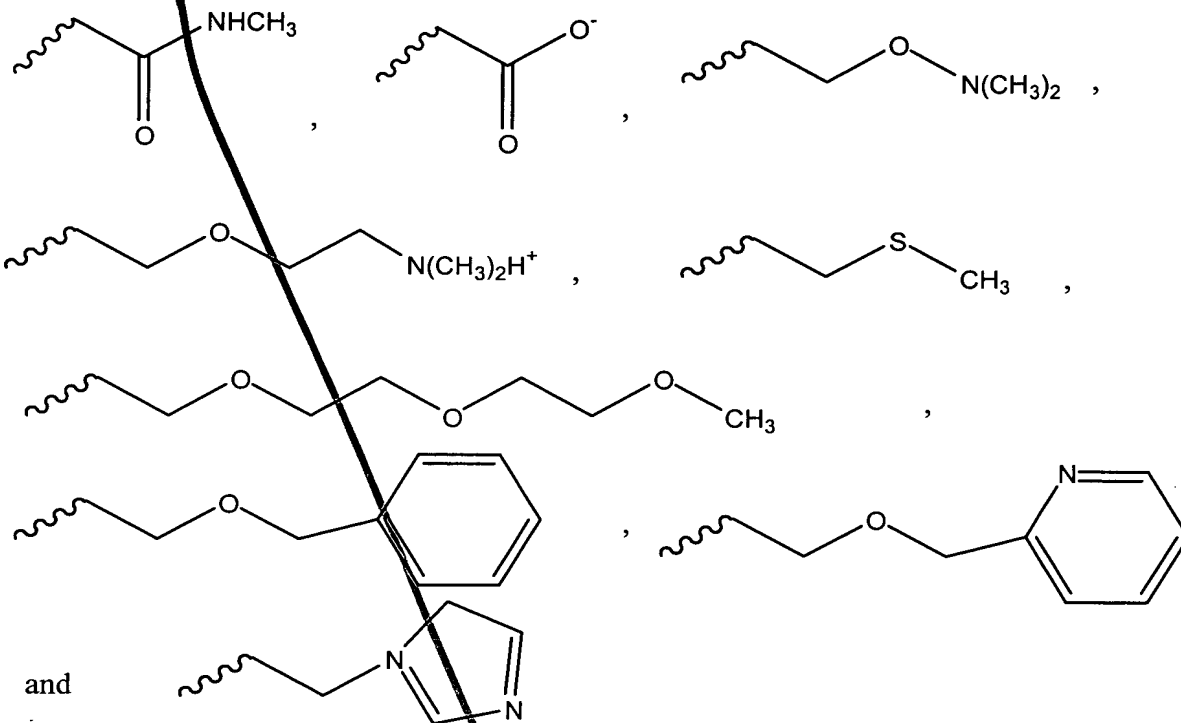
Wherein R¹⁰ is a bond to the sugar, j is O, q is 3'-O-(2-methoxyethyl).

46. The oligonucleotide according to claim 44 wherein said nucleotide is according to structure IV;

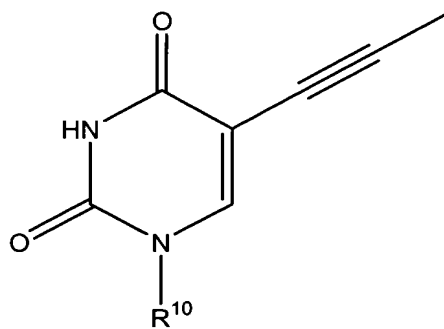


IV

47. The oligonucleotide according to claim 44 where G is oxygen and R¹¹ is selected from the group comprising;



48. The oligonucleotide according to claim 44 wherein the Base is according to structure V;



V

where R¹⁰ is a bond to the sugar.

49. The oligonucleotide according to claim 44 further associated with a pharmaceutically acceptable carrier, diluent, prodrug or lubricant.

50. The oligonucleotide according to claim 44 which is targeted to a nucleic acid encoding mdm2.